Inferring Network Mechanisms: The *Drosophila melanogaster* Protein Interaction Network

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Naturally occurring networks exhibit quantitative features revealing underlying growth mechanisms. Numerous network mechanisms have recently been proposed to reproduce specific properties such as degree distributions or clustering coefficients. We present a method for inferring the mechanism most accurately capturing a given network topology, exploiting discriminative tools from machine learning. The *Drosophila melanogaster* protein network is confidently and robustly (to noise and training data subsampling) classified as a duplication-mutation-complementation network over preferential attachment, small-world, and other duplication-mutation mechanisms. Systematic classification, rather than statistical study of specific properties, provides a discriminative approach to understand the design of complex networks.

1 Introduction

Recent advances in our understanding of biological networks have often focused on understanding the emergence of specific features such as scale-free degree-distributions (*1,2,3*), short mean geodesic lengths or clustering coefficents (*4*). The insights gained into the topological patterns

have motivated various network growth and evolution models in order to determine what simple mechanisms can reproduce the features observed. Among these are the preferential attachment model (*3,5*) exhibiting scale-free degree distributions, and the small-world model (*4*) exhibiting high clustering coefficients and short mean geodesics. Moreover, various duplication-mutation mechanisms have been proposed to describe biological networks (*6,7,8,9,10,11*) and the World Wide Web (*12*). However, in most cases model parameters can be tuned such that multiple models of widely varying mechanisms perfectly fit the motivating real network in terms of single selected features such as the scale-free exponent and the clustering coefficient. Since networks with several thousands of vertices and edges are highly complex, it is also clear that these features can only capture limited structural information.

Here, we make use of *discriminative classification* techniques recently developed in machine learning (*13,14*) to classify a given real network as one of many proposed network mechanisms by enumerating local substructures. Determining what simple mechanism is responsible for a natural network's architecture would (i) facilitate the development of correct priors for constraining network inference and reverse engineering (*15,16,17,18*); (ii) specify the appropriate null model relative to which one evaluates statistical significance (*19,20,21,22,23,24,25,26,27*); (iii) guide the development of improved network models; and (iv) reveal underlying design principles of evolved biological networks. It is therefore desirable to develop a method to determine which proposed mechanism models a given complex network without prior feature selection.

Enumeration of subgraphs has been succesfully used to find network motifs (*19, 20, 21, 22, 23, 24, 25, 26, 27*) during the past few years and is historically a well established method in the sociology community (*28*). Recently, the idea of clustering real networks based on their "significance profiles" has been proposed (*29*). The method assumes randomized networks with fixed degree distribution as the null model to estimate the statistical significance of given subgraphs. The significance profiles are then shown to be similar for various groups of naturally

occurring networks.

Finding statistically significant motifs and clustering can both be characterized as schemes to identify a reduced-complexity description of the networks. We here present an approach which is instead *predictive*, in which labeled graphs of known growth mechanisms are used as training data for a discriminative classifier. This classifier, then, presented with a new graph of interest, can reliably and robustly predict the growth mechanism which gave rise to that graph. Within the machine learning community, such predictive, *supervised learning* techniques are differentiated from descriptive, *unsupervised learning* techniques such as clustering.

We apply our method to the recently-published *Drosophila melanogaster* protein-protein interaction network (*30*) and find that a duplication-mutation-complementation mechanism (*6*) best reproduces *Drosophila*'s network. The classification is robust against noise, even after random rewiring of 45% of the network edges. To validate, we also show that beyond 80% random rewiring the correct (Erdös-Rényi) classification is obtained.

2 Methods

2.1 The data set

We use a protein-protein interaction map based on yeast two-hybrid screening (*30*). Since the data set is subject to numerous false positives, Giot *et al.* assign a confidence score $p \in [0, 1]$, measuring how likely the interaction occurs *in vivo*. In order to exclude unlikely interactions and focus on a core network which retains significant global features, we determine a confidence threshold p^* based on percolation: measurements of the size of the components for all possible values of p^* show that the two largest components are connected for $p^* = 0.65$ (see supplemental material). Edges in the graph correspond to interactions for which $p > p^*$. To reveal possible structural changes in *Drosophila* for less stringent thresholds, we also present results for $p^* = 0.5$ as suggested in (*30*). We remove self-interactions from the network since none

of the proposed mechanisms allow for them. After eliminating isolated vertices the resulting networks consist of 3359 (4625) vertices and 2795 (4683) edges for $p^* = 0.65\ (0.5)$.

2.2 Network mechanisms

We create 7000 graphs as training data, 1000 for each of seven different models drawn from the literature. Every graph is generated with the same number of edges and number of vertices as measured in *Drosophila*; all other existing parameters are sampled uniformly (*31*). The models manifest various simple network mechanisms, many of which explicitly intend to model protein interaction networks.

The duplication-mutation-complementation (*6*) (DMC) algorithm is inspired by an evolutionary model of the genome (*32,33*) proposing that most of the duplicate genes observed today have been preserved by functional complementation. If either the gene or its copy loses one of its functions (edges), the other becomes essential in assuring the organism's survival. There is thus an increased preservation of duplicate genes induced by null mutations. The algorithm features a duplication step followed by mutations that preserve functional complementarity. At every time step one chooses a vertex v at random. A twin vertex v_{twin} is then introduced copying all of v's edges. For each edge of v, one deletes with probability q_{del} either the original edge or its corresponding edge of v_{twin}. The twins themselves are conjoined with an independent probability q_{con}, representing an interaction of a protein with its own copy. Note that no new edges are created by mutations. The DMC mechanism thus assumes that the probability of creating new advantageous functions by random mutations is negligible.

A slightly different implementation of duplication-mutation is realized in (*7*) using random mutations (DMR). Possible interactions between twins are neglected. Instead, edges between v_{twin} and the neighbors of v can be removed with a probability q_{del} and new edges can be created at random between v_{twin} and any other vertices with a probability q_{new}/N, N being the current

total number of vertices. DMR thus emphasizes the creation of new advantageous functions by mutation.

Additionally, we create training data for linear preferential attachment (LPA) networks (*3,5*) (growing graphs with a probability of attaching to previous vertices proportional to $k + a$, a being a constant parameter, and k the degree of the chosen vertex), random static networks (RDS) (*34*) (also known as Erdös-Rényi graphs; vertices are connected randomly), random growing networks (RDG) (*35*) (growing graphs where new edges are created randomly between existing vertices), aging vertex (AGV) networks (*36*) (growing graphs modeling citation networks, where the probability for new edges decreases with the age of the vertex), and small-world (SMW) networks (*4*) (interpolation between regular ring lattices and randomly connected graphs). For descriptions of the specific algorithms we refer the reader to the supplemental material.

2.3 Subgraph census

We quantify the topology of a network by exhaustive subgraph census (*37*) up to a given subgraph size; note that we do *not* assume a specific network randomization nor test for statistical significance as in (*19,20,21,22,23,24,25,26,27*), but we classify network mechanisms using the raw subgraph counts. Rather than choosing most important features a priori, we count all possible subgraphs up to a given cut-off, which can be made either in the number of vertices, number of edges, or the length of a given walk. To show insensitivity to this choice, we present results for two different cut-offs. We first count all subgraphs that can be constructed by a walk of length eight (148 non-isomorphic[1] subgraphs); second, we consider all subgraphs up to a total number of seven edges (130 non-isomorphic subgraphs). Their counts are the input features for our classifier. It is worth noting that the mean geodesic length (average shortest path between

[1]Two graphs are isomorphic if there exists a relabeling of their vertices such that the two graphs are identical.

two vertices) of the *Drosophila* network's giant component is $11.6\ (9.4)$ for $p^* = 0.65\ (0.5)$. Walks of length eight are therefore able to traverse large parts of the network and can also reveal global structures.

2.4 Learning algorithm

Our classifier is a generalized decision tree called an *Alternating Decision Tree* (ADT) (*38*) which uses the Adaboost (*39*) algorithm to learn the decision rules and associate weights to them. Adaboost is a general discriminative learning algorithm proposed in 1997 by Freund and Schapire (*40, 39*), and has since been successfully used in numerous and varied applications (e.g., in text categorization (*41, 42*) and gene expression prediction (*43*)). It is equivalent to an additive logistic regression model (*44*).

An example of an ADT is shown in Figure 1. A given network's subgraph counts determine paths in the tree dictated by inequalities specified by the *decision nodes* (rectangles). For each class, the ADT outputs a real-valued *prediction score*, which is the sum of all weights over all paths. The class with the highest score wins. The prediction score $y(c)$ for class c is related to the probability $p(c)$ for the tested network to be in class c by $p(c) = e^{2y(c)}/(1 + e^{2y(c)})$ (*44*). (The supplemental material gives details on the exact learning algorithm.)

An advantage of ADTs is that they do not assume a specific geometry of the input space; that is, features are not coordinates in a metric space (as in support vector machines or k-nearest-neighbors classifiers), and the classification is thus independent of normalization. The algorithm assumes neither independence nor dependence among subgraph counts. The features distinguish themselves solely by their individual abilities to discriminate different classes.

3 Results

We perform cross-validation (*31, 13*) with multi-class ADTs, thus determining an empirical estimate of the generalization error, the probability of mislabeling an unseen test datum. The confusion matrix in Table 1 shows truth and prediction for the test sets. Five out of seven classes have nearly perfect prediction accuracy. Since AGV is constructed to be an interpolation between LPA and a ring lattice, the AGV, LPA and SMW mechanisms are equivalent in specific parameter regimes and correspondingly show a non-negligible overlap. Nevertheless, the overall prediction accuracy on the test sets still lies between 94.6% and 95.8% for different choices of p^* and subgraph size cut-off. Note that preferential attachment is completely distinguishable from duplication-mutation despite the fact that a duplication mechanism introduces an *effective* preferential attachment (*31, 45*). Even models that are based on the same fundamental mechanism, like duplication-mutation in DMC and DMR, are perfectly separable. Only small algorithmic changes in network mechanisms can thus give rise to easily detectable differences in substructures. Figure 4 confirms that although many of these models have similar degree distributions, clustering coefficients, or mean geodesic lengths, they have indeed distinguishable topologies.

Figure 1 shows the first few decision nodes (out of 120) of a resulting ADT. The prediction scores reveal that a high count of 3-cycles suggest a DMC network (node 3). The DMC mechanism indeed facilitates the creation of many 3-cycles by allowing two copies to attach to each other, thus creating 3-cycles with their common neighbors. In particular a few combinations are good predictors for some classes. For example, a low count in 3-cycles but a high count in 8-edge linear chains is a good predictor for LPA and DMR networks (nodes 3 and 4). Due to the sparseness of the networks the preferential attachment does not lead to a clustered structure. While LPA readily yields hubs, cycles are less probable. (More detailed ADTs can be viewed

in the supplemental material.)

Having built a classifier enjoying good prediction accuracy, we can now determine the network mechanism that best reproduces the *Drosophila* protein network (or in priniciple any network of same size) using the trained ADTs for classification. Table 2 gives the prediction scores of the *Drosophila* network for each of the seven classes, averaged over folds.

The duplication-mutation-complementation mechanism is the only class having a positive prediction score in every case. In particular for $p^* = 0.65$ the DMC classification has a high score of 8.2 and 8.6. Also, the comparatively small standard deviations over different folds indicate robustness of the classification against data subsampling. While the high rankings of both duplication-mutation classes confirm our biological understanding of protein network evolution, our findings strongly support an evolution restricted by functional complementarity over an evolution that creates and deletes functions at random.

Interestingly for $p^* = 0.65$ the RDG mechanism of random growth (edges are connected randomly between existing vertices) has a higher prediction score than the LPA or AGV growing graph mechanisms. Growth without any underlying mechanism other than chance therefore generates networks closer in topology to the core network ($p^* = 0.65$) of *Drosophila* than growth governed by preferential attachment. We also emphasize that the small-world *character* of high clustering and short mean geodesic length, often attributed to biological networks (*30, 46*), is not enough to conclude that the given network is close to the small-world *model* (*4*) (an interpolation between regular ring lattices and randomly connected graphs), as shown here. The classification for $p^* = 0.5$ is less confident probably due to the additional noise present in the data when including low p-value (improbable) interactions, as we discuss below.

While not necessary for the classification itself, visualizing subgraph profiles can give a qualitative and more intuitive way of interpreting the classification result and a better understanding of the topological differences between *Drosophila* and each of the seven mechanisms.

We plot in Figure 3 their color-coded subgraph counts, averaged over all 1000 realizations of every model, for a representative subset of 50 subgraphs[2]. We group together subgraphs (indicated by black lines) that exhibit the smallest absolute difference between the average subgraph count for the model, and for *Drosophila*. For 60% of the subgraphs (S1-S30), *Drosophila*'s counts are closest to DMC's. All of these subgraphs contain one or more cycles, including highly connected subgraphs such as K_4 (S1)[3], and long linear chains ending in cycles (S16, S18, S22, S23, S25). DMC is the only mechanism that can give rise to the high occurrences of cycles measured in *Drosophila*. Owing to the networks' sparseness cyclic structure is unlikely to be generated in LPA, AGV, SMW, and RDS. The models LPA and AGV, however, are close to *Drosophila*'s topology according to subgraphs S44-S50 featuring open-ended chains and hubs, which occur frequently in both models as well as in *Drosophila*.

Since yeast two-hybrid data is known to be susceptible to numerous errors (*30*), proposed inference methods are only reliable if they are robust against noise. To confirm that our method shows this property, we classify the *Drosophila* network for various levels of artificially-introduced noise by replacing existing edges with random ones. Figure 5 shows the prediction scores for all seven classes as functions of the fraction of edges replaced. As validation, the network is correctly classified as an RDS graph when all edges are randomized. About 30% of *Drosophila*'s edges can be replaced without seeing any significant change in all seven prediction scores, and about 45% can be replaced before *Drosophila* is no longer classified as a DMC network. At this point the prediction scores of DMC, DMR and AGV are very close, which is also observed for the prediction scores for $p^* = 0.5$ (see Table 2), where they rank top three in this order. The results therefore suggest that the less confident classification for $p^* = 0.5$ could be mainly due to the presence of more noise in the data after inclusion of low p-value edges.

We have presented a method to infer growth mechanisms for real networks. Advantageous

[2]We refer to the supplemental material for the whole set of 148 subgraphs

[3]a completely connected subgraph of four nodes

properties include robustness both against noise and data subsampling, and the absence of any prior assumptions about which network features are important. Moreover, since the learning algorithm does not assume any relationships among features, the input space can be augmented with various features in addition to subgraph counts. We find that the *Drosophila* protein interaction network is confidently classified as a DMC network, a result which strongly supports ideas presented by Vazquez *et al.* (*6*) and Force *et al.* (*33*) about the nature of genetic evolution. Recently, Wang *et al.* presented direct experimental evidence for a single DMC event in *Drosophila melanogaster* (*47*). We anticipate that further use of machine learning techniques will answer a number of questions of interest in systems biology.

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		PREDICTION						
		DMR	DMC	AGV	LPA	SMW	RDS	RDG
	DMR	99.3%	0.0%	0.0%	0.0%	0.0%	0.1%	0.6%
	DMC	0.0%	99.7%	0.0%	0.0%	0.3%	0.0%	0.0%
	AGV	0.0%	0.1%	84.7%	13.5%	1.2%	0.5%	0.0%
TRUTH	LPA	0.0%	0.0%	10.3%	89.6%	0.0%	0.0%	0.1%
	SMW	0.0%	0.0%	0.6%	0.0%	99.0%	0.4%	0.0%
	RDS	0.0%	0.0%	0.2%	0.0%	0.8%	99.0%	0.0%
	RDG	0.9%	0.0%	0.0%	0.1%	0.0%	0.0%	99.0%

Table 1: **Confusion matrix** for tested networks using five-fold cross-validation (*13*). Entries (i, j) show the probability of predicting class j given that the true class is i. The training data is based on the size of the *Drosophila* protein network with a confidence treshold of $p^* = 0.5$, the input features of the classifier being counts of all possible walks of length eight. The overall prediction accuracy is 95.8%. Prediction errors among AGV, LPA and SMW networks are due to equivalence of the models in specific parameter regimes.

	8-edge-walk subgraphs $p^* = 0.65$		subgraphs with up to 7 edges $p^* = 0.65$		8-edge-walk subgraphs $p^* = 0.5$	
RANK	CLASS	SCORE	CLASS	SCORE	CLASS	SCORE
1	DMC	8.2 ± 1.0	DMC	8.6 ± 1.1	DMC	0.8 ± 2.9
2	DMR	-6.8 ± 0.9	DMR	-6.1 ± 1.7	DMR	-2.1 ± 2.0
3	RDG	-9.5 ± 2.3	RDG	-9.3 ± 1.6	AGV	-3.1 ± 2.2
4	AGV	-10.6 ± 4.2	AGV	-11.5 ± 4.1	LPA	-10.1 ± 3.1
5	LPA	-16.5 ± 3.4	LPA	-14.3 ± 3.2	SMW	-20.6 ± 1.9
6	SMW	-18.9 ± 0.7	SMW	-18.3 ± 1.9	RDS	-22.3 ± 1.7
7	RDS	-19.1 ± 2.3	RDS	-19.9 ± 1.5	RDG	-22.5 ± 4.7

Table 2: **Prediction scores for the *Drosophila* protein network** for different confidence thresholds p^* and different cut-offs in subgraph size. *Drosophila* is consistently classified as a DMC network, with an especially strong prediction for a confidence threshold of $p^* = 0.65$ and independently of the cut-off in subgraph size.

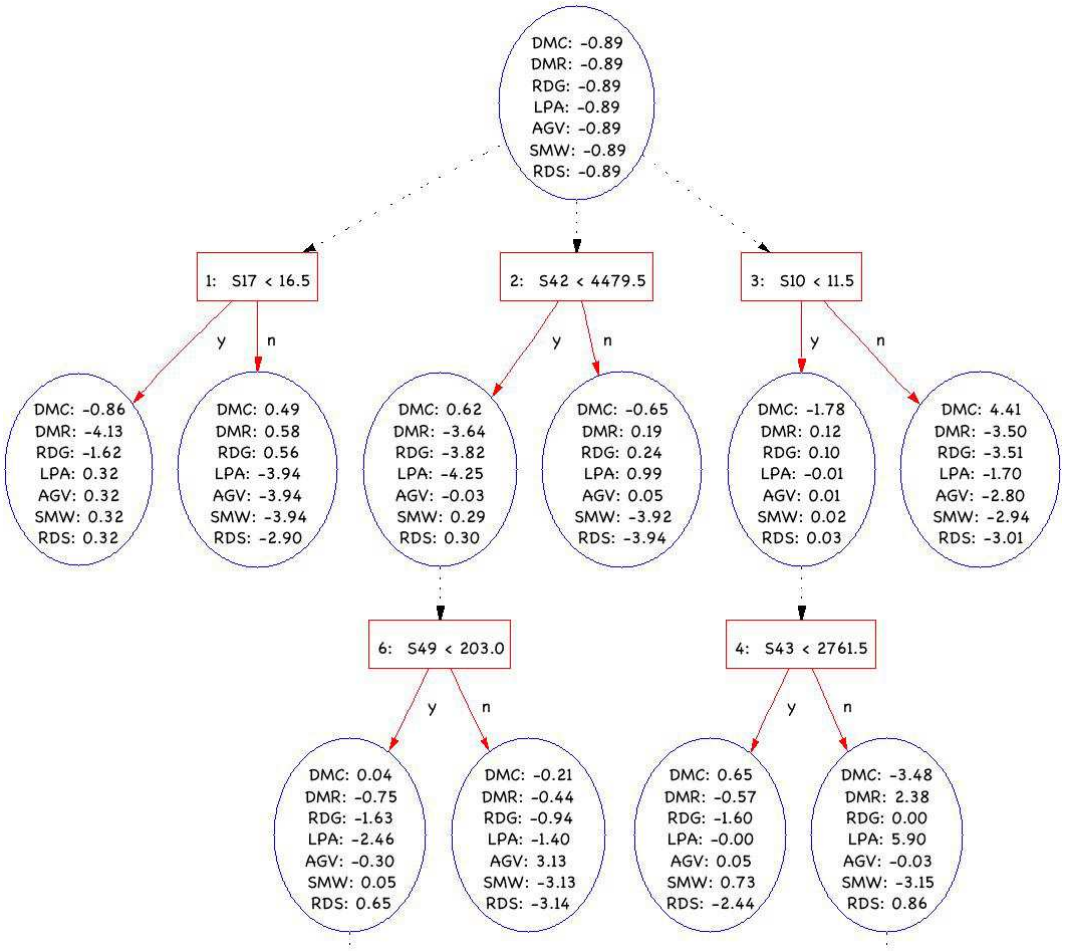


Figure 1: **Alternating decision tree:** The first few nodes of one of the trained ADTs are shown. At every boosting iteration one new decision node (rectangle) with its two prediction nodes (ovals) is introduced. Every test network follows several paths in the tree dictated by inequalities in the decision nodes (S# refers to a specific subgraph count; see Figure 2.). The final score is the sum of all prediction scores over all paths and the class with the highest prediction score wins.

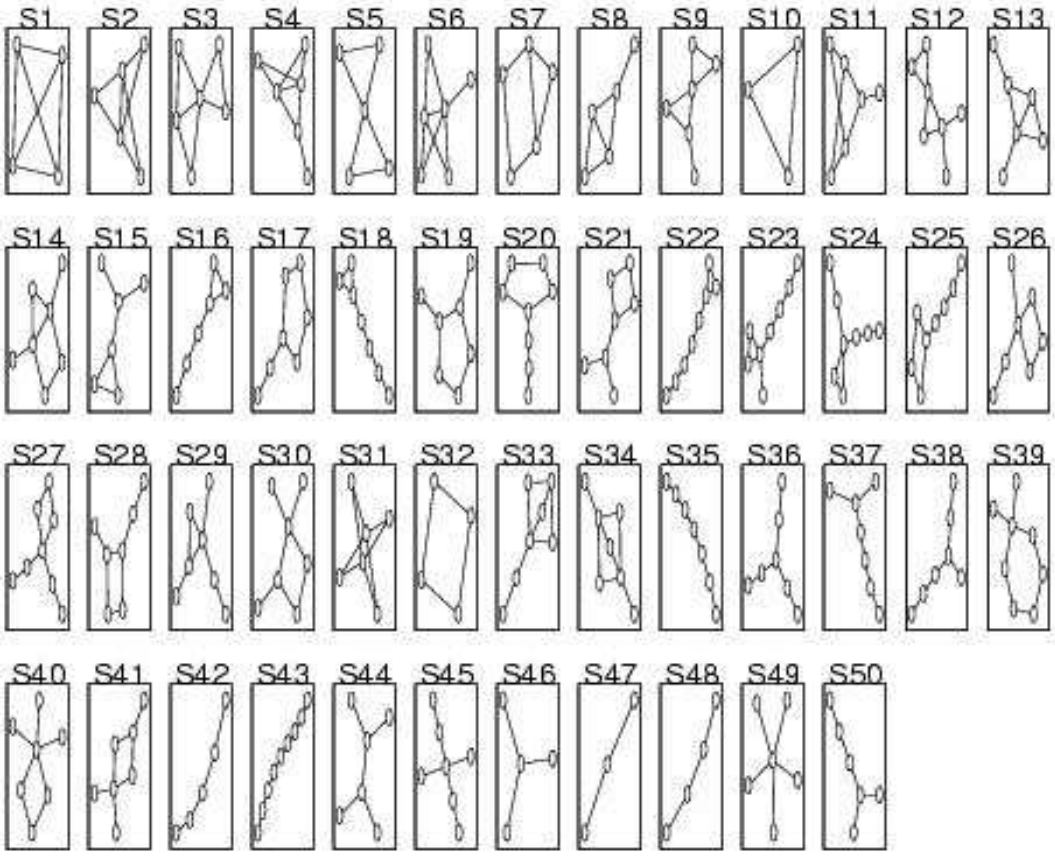


Figure 2: **Subgraphs associated with Figures 3 and 1.** A representative subset of 50 subgraphs out of 148 is shown.

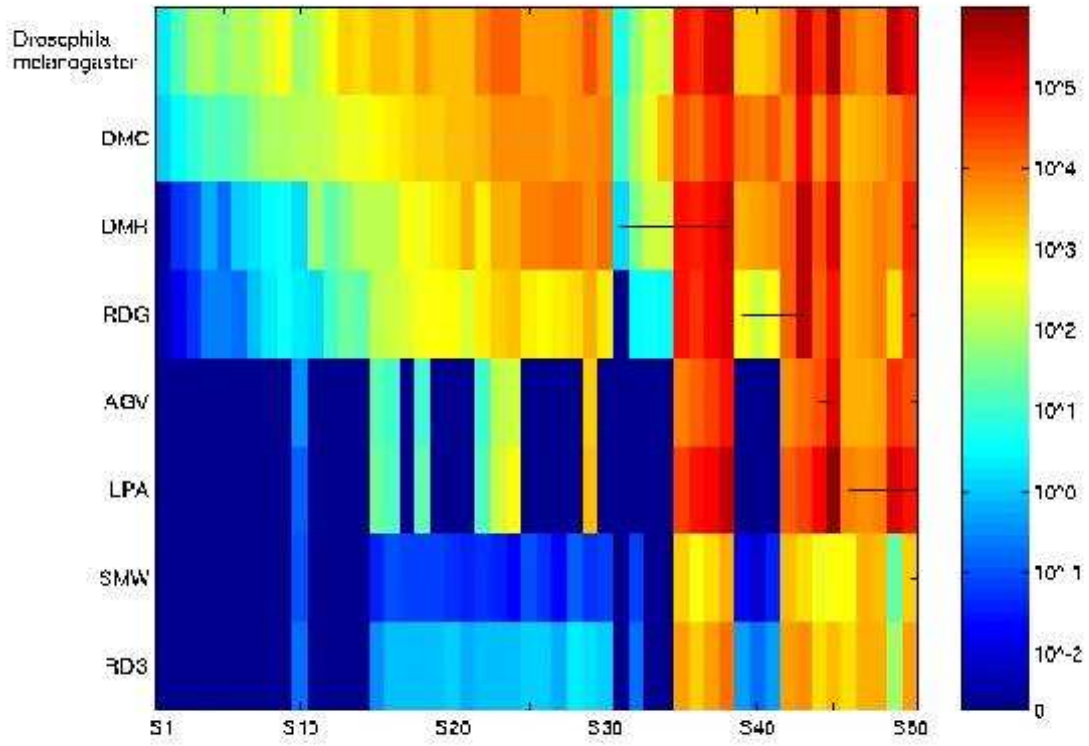
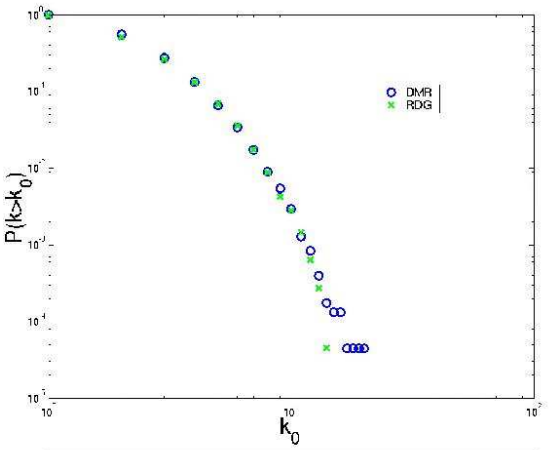
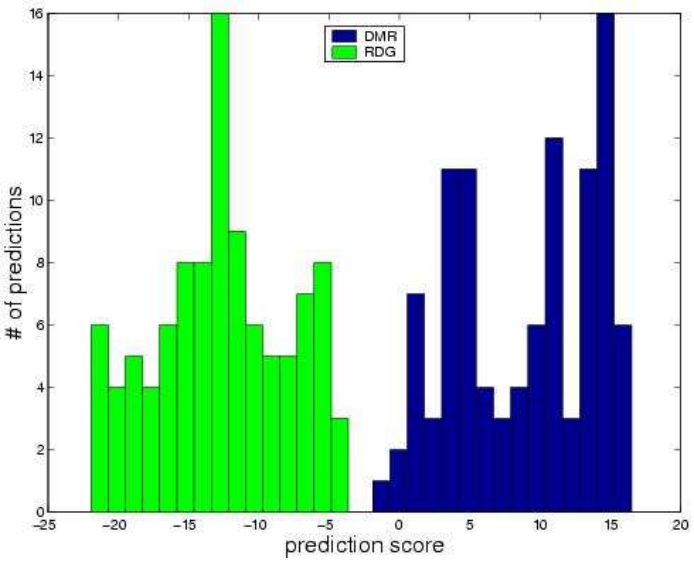


Figure 3: **Subgraph profiles.** The average subgraph count of the training data for every mechanism is shown for 50 representative subgraphs. The labels S1-S50 refer to Figure 2. Black lines indicate that this model is closest to *Drosophila* based on the absolute difference between the subgraph counts.



	DMR	RDG
$\langle C \rangle$	$2.6\ 10^{-4} \pm 1.3\ 10^{-4}$	$5.4\ 10^{-4} \pm 3.7\ 10^{-4}$
$\langle L \rangle$	10.4 ± 0.1	9.6 ± 0.04

(a)



(b)

Figure 4: **Discriminating similar networks:** Ten graphs of two different mechanisms exhibit similar average geodesic lengths and almost identical degree dstribution and clustering coefficients. **(a)** cumulative degree distribution $p(k > k_0)$, average clustering coefficient $\langle C \rangle$ and average geodesic length $\langle L \rangle$, all quantities averaged over a set of ten graphs. **(b)** prediction scores for all ten graphs and all five cross-validated (*13*) ADTs. The two sets of graphs can be perfectly separated by our classifier.

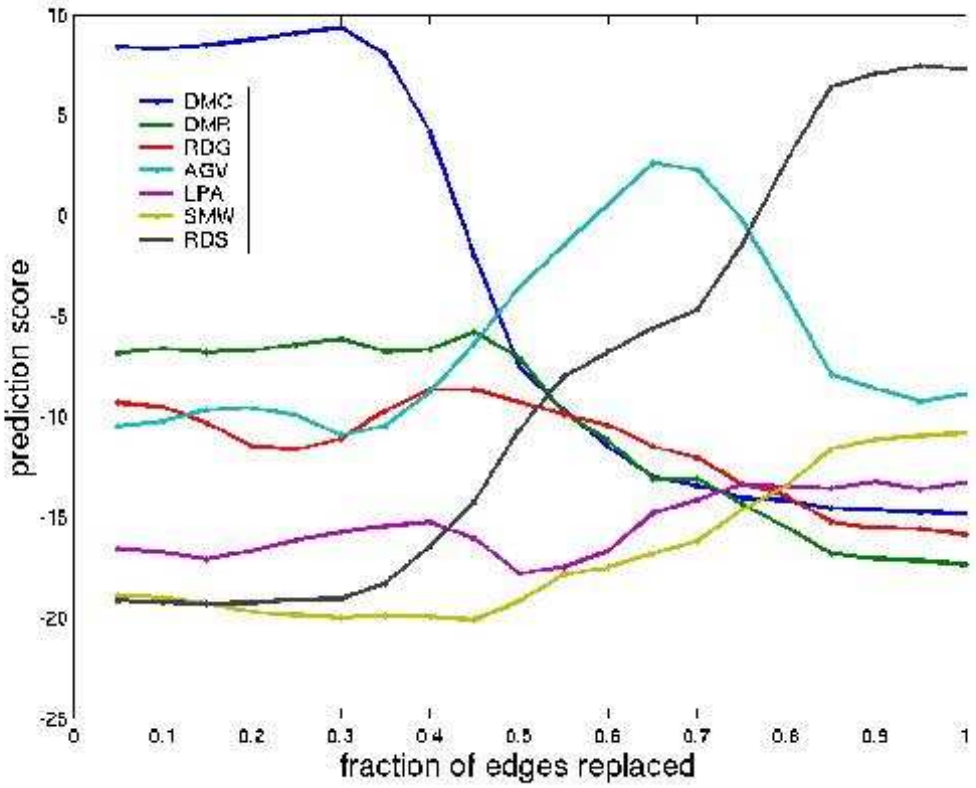


Figure 5: **Robustness against noise:** Edges in *Drosophila* are randomly replaced and the network is reclassified. Plotted are prediction scores for each of the seven classes as more and more edges are replaced. Every point is an average over 200 independent random replacements. For high noise levels (beyond 80%) the network is classified as an Erdös-Rényi (RDS) graph. Also note that the confidence in the classification as a DMC network for low noise (less than 30%) is even higher than in the classification as an RDS network for high noise. The prediction score $y(c)$ for class c is related to the estimated probability $p(c)$ for the tested network to be in class c by $p(c) = e^{2y(c)}/(1 + e^{2y(c)})$ (*44*).